REMARKS

In response to the Non-Final Office Action mailed May 17, 2010, and having a period for response set to expire on August 17, 2010, Applicant respectfully requests that the Examiner favorably consider the following remarks.

Amendments to the claims

With the present submission, claims 18 and 40 have been amended. Claims 1-17 and 21-32 were previously canceled without prejudice. Thus, claims 18-20 and 33-49 are presently under consideration. Specifically, in claims 18 and 40, part (b) has been amended to recite "each strand is independently 18 to 24 nucleotides in length". This amendment is supported by the instant specification as filed and the priority applications of record and does not add new matter. Entry is respectfully requested.

Priority

The Office declined to award the instant claims a priority earlier than the filing date of the instant application because "None of the prior-filed applications teach the following limitations: a siNA molecule wherein each strand is 18-24 nucleotides in length and the nucleic acid molecule comprises between 17 and 23 base pairs; in combination with each of the instantly recited modifications". Office Action, page 3. Applicant respectfully traverses the Office's priority determination.

The claimed length of 18-24 and 17 to 23 base pairs found previously in claims 18 and 40 subpart (b) find literal support in each of the priority applications relied upon by the Applicant (see for example page 22, lines 12-15 of the '580 provisional application filed on February 20, 2002:

> *In one embodiment of the present invention, each sequence of a siNA molecule of the invention is independently 18 to 24 nucleotides in length, in specific embodiments about 18, 19, 20, 21, 22, 23, or 24 nucleotides in length. In another embodiment, the siNA duplexes of the invention independently comprise about 17 to about 23 base pairs (e.g., about 17, 18, 19, 20, 21, 22 or 23).*

The cited passage clearly defines the overall length and base pair parameters of *any siNA molecule of the invention* and is not limited to any particular structure or configuration. In addition, contrary to the Office's interpretation, the first and second sentences of the cited paragraph are not mutually exclusive and do not necessarily refer to separate molecules merely because of the use of the term "another embodiment". Clearly, this language embraces double stranded nucleic acid molecules having strands of defined lengths with a defined number of base pairs, features that necessarily flow from each other and which are not mutually exclusive. Nevertheless, without acquiescing to the Office's position and in the interest of advancing prosecution and putting the claims in better condition for allowance or appeal, Applicant has amended claims 18 and 40 as described above.

For the reasons stated above and as supported by the prosecution history, including the detailed showing of support throughout the chain of priority as set forth in the response of April 22, 2010, the instant claims clearly have literal support and are fully enabled by all of the following priority applications: parent application USSN 10/444,853, filed May 23, 2003; PCT/US03/05346, filed February 20, 2003; provisional application 60/408,378, filed September 5, 2002; provisional application 60/386,782, filed June 6, 2002; and provisional application 60/358,580, filed February 20, 2002.

Claim Rejections – 35 U.S.C. 112

The Office rejected claims 18-20 and 33-49 under 35 U.S.C. 112 first paragraph as allegedly being drawn to new matter. Claims 18 and 40 have been amended as described above. As with the issue of priority, Applicant finds literal support for the instantly claimed invention and has previously pointed to numerous representative examples of the claimed double stranded nucleic acid molecules that have been synthesized and tested for RNAi activity in both the application as filed and the priority applications. As such, Applicant respectfully maintains that the disclosure of the priority applications relied upon not only "reasonably conveys to the artisan that the inventor had possession at that time of the later claimed subject matter", but also contains "a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains or with which it is most nearly connected, to make and use the same". *Ralston*

Purina Co. v. Far-Mar-Co, Inc., 772 F.2d 1570, 1575 (Fed. Cir. 1985) and 35 U.S.C. § 112, ¶ 1 respectively. Withdrawal of the rejection is respectfully requested.

Claim Rejections – 35 U.S.C. 103(a)

The Office rejected claims 18-20 and 33-49 under 35 U.S.C. 103(a) as allegedly being obvious over Elbashir (EMBO J., 2001, 20(23):6877) in view of Matulic-Adamic (US 5,998,203), Parrish (Molecular Cell, 2000, 6:1077-87), and Crooke (US 5,898,031). Applicant respectfully traverses the rejection.

Applicant maintains that at the time of the invention, Elbashir et al. effectively taught away from one of skill in the art making and using siRNA duplexes that are more extensively modified compared to the duplexes shown in Figure 4 of the Elbashir reference that were shown to be capable of maintaining RNAi activity. Elbashir et al. described siRNA duplexes having limited 2'-deoxy substitutions in the 3'-overhang regions of a siRNA duplex. Figure 4 shows that when the two, overhanging 3' nucleotides of each strand were modified, RNAi activity was maintained. The same result was found when the two additional nucleotides adjacent to the 3' overhangs of each strand were modified. However, when either one strand of the duplex was modified or both strands of the duplex were modified, RNAi activity was abolished. The authors summarize their findings in the Discussion section of the paper in a "user guide" to those skilled in the art for generating siRNA duplexes that are both effective at gene silencing and more palatable from a manufacturing cost perspective. The authors state on page 6885, with emphasis added, the following:

> *Efficiently silencing siRNA duplexes are composed of 21 nt sense and 21 nt antisense siRNAs and must be selected to form a 19 bp double helix with 2 nt 3'-overhanging ends. 2'-deoxy substitutions of the 2 nt 3'-overhanging ribonucleotides do not affect RNAi, but help to reduce the costs of RNA synthesis and may enhance RNase resistance of siRNA duplexes.* ***More extensive 2'-deoxy or 2'-O-methyl modifications reduce the ability of siRNAs to mediate RNAi, probably by interfering with protein association for siRNP assembly.***

It should be noted that the teachings of the Elbashir reference have been reviewed by the BPAI who find that "[a] fair reading of [Elbashir]…is that more extensive 2'-deoxy or 2'-O-

methyl modifications beyond the two nucleotide 3'-overhang reduces the ability of siRNAs to mediate RNAi". Appeal 2009-002562, at page 27. This fair reading is consistent with the position that more extensive modification beyond the 3'-terminal regions of one or both strands of a siRNA molecule is either expressly taught away from, or in the alternative, is highly unpredictable in view of the teachings of Elbashir et al. who premise their conclusion on mechanistic grounds, i.e. the premise that more extensive modifications interfere with protein association for siRNP assembly. The present claims require 10 or more modified pyrimidine nucleotides in the sense and antisense strands (claim 18) or alternately 10 or more modified pyrimidine nucleotides in the sense or antisense strand (claim 40). The claims also require terminal caps at both 5' and 3' ends of the sense strand, in addition to a terminal cap at the 3'-end of the antisense strand. Clearly, one of skill in the art at the time of the invention, having read the teachings of Elbashir that warn against more extensive modification beyond the 3'-terminal regions due to proposed mechanistic concerns over the ability of the siRNA to associate with proteins required for RNAi, and who explicitly show that more extensive modification of the siRNA duplex result in abolished RNAi activity, would certainly not have any reasonable expectation of success in envisioning active molecules with modifications as are presently claimed.

Parrish, does nothing to remedy the shortcomings of the Elbashir reference. Importantly, the Elbashir reference and the Parrish reference share several common authors, with publication of the Parrish reference preceding the publication of the Elbashir reference. Nevertheless, even in view of their prior work in long dsRNA, the Elbashir authors still failed to apply "more extensive" modifications when attempting to optimize the stability and activity of siRNA and concluded that more extensive modification beyond the 3'-termini results in reduced RNAi activity in short interfering RNA (siRNA) molecules. Together, the Elbashir and Parrish references provide strong teaching away from, and such a high level of unpredictability, so as to preclude one of skill in the art (as demonstrated by the authors themselves) from arriving at or practicing the instantly claimed invention.

The Crooke reference, which describes modification of antisense gapmer molecules and which precedes both Parrish and Elbashir does nothing to remedy the teaching away and lack of

predictability resulting from a plain reading of Elbashir's teachings with respect to "more extensive" modification of siRNA. Clearly, the modifications as instantly claimed are "more extensive" because they would necessarily extend well beyond any 3'-overhang regions of the claimed double stranded nucleic acid molecules. Because the teachings of Elbashir's "user guide" are cumulative with respect to chemical modification of siRNA, and because the teachings of Elbashir propose that RNAi activity of more extensively modified siRNA is compromised via mechanism (i.e., by interfering with protein association for siRNP assembly), one of skill in the art would simply not have any reasonable expectation of success in practicing the instant invention until reading Applicant's own disclosure. As such, the Office appears to be basing the instant rejection on inappropriate hindsight in view of the Applicant's own disclosure. Withdrawal of the rejection is respectfully requested.

Claim Rejections – Double Patenting

The Office provisionally rejected claims 18-20 and 33-49 as allegedly being unpatentable on the ground of non-statutory obviousness-type double patenting over claims 33-50 of co-pending Application No. 10/923,536. Application 10/923,536 is presently abandoned. Withdrawal of the rejection is respectfully requested.

Conclusion

In view of the foregoing, Applicant respectfully submits the pending claims are in condition for allowance. If the Examiner believes a telephone conference would expedite prosecution of this application, she is urged to telephone the undersigned at the telephone number below.

Respectfully submitted,

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